PATENT ABSTRACTS OF JAPAN

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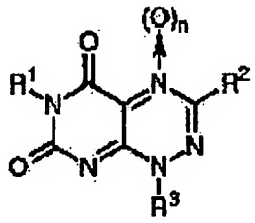
(54) ANTITUMOR AGENT

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a new orally or parenterally administrable antitumor agent having excellent antitumor activity by conducting a pharmaceutical manufacturing of a specific 7-azapteridine derivative as active ingredient together with a medicinal support in common use.

SOLUTION: This antitumor agent having excellent antitumor activity is obtained by conducting a pharmaceutical manufacturing of a 7-azapteridine derivative of the formula [R1 is phenyl or a lower alkyl; R2 is (substituted) phenyl or 2-phenylethenyl; R3 is a lower alkyl or cycloalkyl; (n) is 0 or 1] {e.g. 3-(2-hydroxyphenyl)-1,6-dimethylipirimido[5,4-e]-1,2,4-triazine-5,7(1H, 6H)-dione} as active ingredient together with a medicinal support, vehicle binder, lubricant, etc., into tablets, granules, capsules, injections etc.



LEGAL STATUS

[Date of request for examination] 20.02.2003

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than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

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[Date of requesting appeal against examiner's decision of rejection]

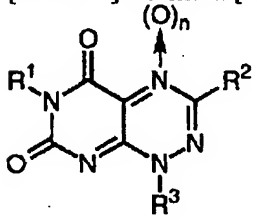
[Date of extinction of right]

* NOTICES *

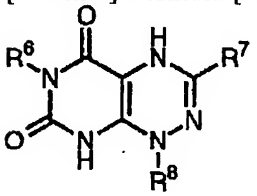
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] Formula [** 1]



R1 shows a phenyl group or a low-grade alkyl group among [type. R2 "low-grade alkyl group, A halogen atom, a hydroxyl group, a lower alkoxy group, a methylene dioxy radical, and formula -NR four R5 (R4 and R5 show a hydrogen atom or a low-grade alkyl group among a formula, respectively.) the phenyl group or 2-phenyl ethenyl radical which may be permuted by one of the radicals chosen from the group which consists of a radical expressed", or two is shown, R3 shows a low-grade alkyl group or a cycloalkyl radical, and n shows 0 or 1.] The antitumor agent which comes out and makes an active principle the 7-aza-pteridine derivative expressed.
[Claim 2] Formula [** 2]



[-- the inside of a formula, and R6 -- a low-grade alkyl group -- being shown -- R7 -- a low-grade alkyl group -- or -- "-- a methylene dioxy radical or formula [ ] -- the phenyl group which may be permuted by radical" expressed with -NR nine R10 (R9 and R10 show a hydrogen atom or a low-grade alkyl group among a formula, respectively.) is shown, and R8 shows a low-grade alkyl group.] The antitumor agent which comes out and makes an active principle the 7-aza-pteridine derivative expressed.

[Translation done.]

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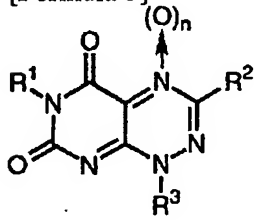
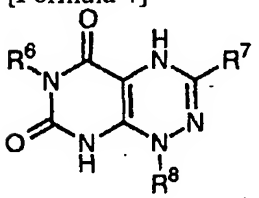
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the antitumor agent which makes a 7-aza-pteridine derivative an active principle.
[0002]
[Description of the Prior Art] Although many of compounds of this invention are well-known compounds by JP,7-41479,A, Chem.Pharm.Bull., 23 volumes, No. 9, 2001-2009 pages (1975), J.C.S.PerkinI, 713 pages (1976), Chem.Pharm.Bull., 41 volumes, No. 2, 362-368 pages (1993) or Synthesis, and No.3,177-179 page (1975) one of reference, The antitumor action is not known.
[0003]
[Problem(s) to be Solved by the Invention] The purpose of this invention is to offer the outstanding antitumor agent.
[0004]
[Means for Solving the Problem] As a result of advancing research wholeheartedly for achievement of said technical problem, this invention persons found out having the antitumor action excellent in a certain kind of 7-aza-pteridine derivative, and completed this invention.
[0005] That is, this invention is a formula. [0006]
[Formula 3]



(I)

[0007] R1 shows a phenyl group or a low-grade alkyl group among [type. R2 "low-grade alkyl group, A halogen atom, a hydroxyl group, a lower alkoxy group, a methylene dioxy radical, and formula -NR four R5 (R4 and R5 show a hydrogen atom or a low-grade alkyl group among a formula, respectively.) the phenyl group or 2-phenyl ethenyl radical which may be permuted by one of the radicals chosen from the group which consists of a radical expressed", or two is shown, R3 shows a low-grade alkyl group or a cycloalkyl radical, and n shows 0 or 1.] It is the antitumor agent which comes out and makes an active principle the 7-aza-pteridine derivative expressed, and this invention is a formula. [0008]
[Formula 4]



(II)

[0009] [-- the inside of a formula, and R6 -- a low-grade alkyl group -- being shown -- R7 -- a low-grade alkyl group -- or -- "-- a methylene dioxy radical or formula [ ] -- the phenyl group which may be permuted by radical" expressed with -NR nine R10 (R9 and R10 show a hydrogen atom or a low-grade alkyl group among a formula, respectively.) is shown, and R8 shows a low-grade alkyl group.] It is the antitumor agent which comes out and makes an active principle the 7-aza-pteridine derivative expressed.

[0010] In this invention, a low-grade alkyl group is the thing of the shape of the shape of a straight chain of 1-4 carbon atomic numbers, and a branched chain, for example, are a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, t-butyl, etc.

[0011] Moreover, a lower alkoxy group is the thing of the shape of the shape of a straight chain of 1-4 carbon atomic numbers, and a branched chain, for example, are a methoxy group, an ethoxy radical, a propoxy group, a butoxy radical, etc. A cycloalkyl radical is a cyclopentylic group, a cyclohexyl radical, or a cycloheptyl radical. A halogen atom is a chlorine atom, a bromine atom, or an iodine atom.

[0012] The compound used as the active principle of the antitumor agent of this invention can be easily manufactured like the approach of a publication at said well-known reference according to the approach of a publication in said well-known reference. Moreover, the compound of a formula (II) can obtain toxoflavins by reacting with sodium dithionite.

[0013] the compound concerning this invention -- a conventional method -- as pharmaceutical preparation, such as a tablet, a granule, powder, a capsule, and injections, -- internal use -- or parenteral administration is carried out. In manufacture of the above-mentioned pharmaceutical preparation, support (for example, crystalline cellulose, starch, a lactose, a mannitol, etc.) in ordinary use, for example, excipients, a binder, lubricant (for example, hydroxypropylcellulose, a polyvinyl pyrrolidone, etc.) (for example, magnesium stearate, talc, etc.), etc. are used. Although the dose of the antitumor agent of this invention changes with a patient's symptom, age, sex, purposes of a therapy, etc., it is usually 1-1000mg in an adult.

[0014]

[Example(s) of Experiment] Hereafter, the example of an experiment is given and the effectiveness of the antitumor agent of this invention is further explained to a detail.

In 1, 2, 4-triazine -5, and a 7(1H, 6H)-dione [type (I) -1 and example of manufacture 13-(2-hydroxyphenyl) pyrimide [6-dimethyl] [5 and 4-e] - R -- one -- a methyl group -- R -- two -- two - hydroxyphenyl -- a radical -- R -- three -- a methyl group -- n -- zero -- it is -- a compound -- the following -- a compound -- one --] -- and -- three - (2-hydroxyphenyl) -1, 6-dimethyl pyrimide [5, and 4-e --] - 1, 2, 4-triazine -5, and 7(1H, 6H)-dione In a 4-oxide [type (I) R -- one -- a methyl group -- R -- two -- two - hydroxyphenyl -- a radical -- R -- three -- a methyl group -- n -- one -- it is -- a compound -- the following -- a compound -- two --] -- manufacture -- (-- one --) -- three - methyl - six - (1-methyl hydrazino) -- a uracil (20mmol) -- dry ethanol (100ml) -- dissolving -- The 2-hydroxy benzaldehyde (40mmol) was added and it stirred at the room temperature for 2 hours. The generated solid-state was separated after reaction termination, it recrystallized in dry ethanol, and the 6-[2-(2-hydroxy benzylidene)-1-methyl hydrazino]-3-methyl uracil (4.83g) was obtained as colorless needle crystal.

m. p.253-255 degrees C.

[0015] The compound (15mmol) obtained by (2) and (1) was suspended in the acetic acid (50ml), and sodium nitrite (3.1g, 45mmol) was added small quantity every after cooling at 5-7 degrees C. It stirred at the room temperature further after addition for 6 hours. The generated solid-state was separated after reaction termination, and it rinsed and dried. When diethylether (100ml) was added to the mother liquor, the crystal deposited further. This was separated, this second crystal and first crystal that rinsed and dried were set, separation purification of two kinds of components was carried out with the silica gel column chromatography (benzene: expansion solvent; ethyl acetate = 9:1), each was recrystallized from the dioxane water solution 40%, and the compound of two sorts of marks was obtained.

Compound 1[m. p.200 - 202-degree-C(orange needle crystal)]

Compound 2[m. p.194 - 196-degree-C(yellow needle crystal)].

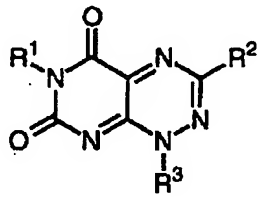
[0016] The manufacture toxoflavins (5mmol) of the compound of example of manufacture 2 formula

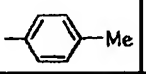
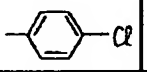
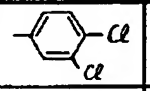
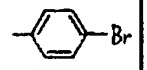
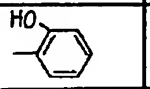
(II) were added to the water solution (30ml) of sodium dithionite (2.6g, 15mmol), and it stirred for 10 minutes at the room temperature. The deposit crystal was separated after reaction termination and the mark compound was obtained by carrying out reduced pressure drying within an after [rinsing] desiccator. The melting point of the manufactured compound is shown in Table 4.

[0017] The cell suspension (it floats to a fetal-calf-serum addition MEM culture medium 10%) of 2x103 HT1080 cells / 100microl which carried out subculture to each hole of 96 hole plate of the example flat bottom of an experiment was added, and it cultivated for 24 hours. To this, it dissolved in dimethyl sulfoxide, the specimen [this invention compound liquid 100microl (the 0.5% of the dimethyl sulfoxide last concentration)] diluted with the culture medium was added, and it cultivated to it for further 72 hours. MTT [3-(4, 5-dimethyl thiazole-2-IRU)-2 and 5-diphenyl teterazolium bromide] (color reagent) was added after culture, and it cultivated for further 4 hours. After culture termination, except for the culture medium, the cell was dissolved in the dimethyl sulfoxide of 150microl, and the absorbance of 540nm was measured. It asked for the ratio of the absorbance of the specimen processing group to the absorbance of a control group, and growth inhibition concentration (IC50 value) was calculated 50%. The experimental result of the typical compound concerning this invention was shown in Table 1 - 4.

[0018]

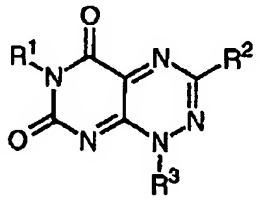
[Table 1]

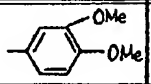
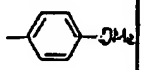
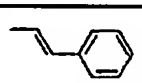
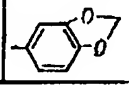


R^1	R^2	R^3	IC_{50}値(μg/ml)
Ph		Me	0.66
Ph		Me	0.76
Ph		Me	2.45
Ph		Me	1.71
Me		Me	0.21
Me	Ph	Me	0.59
Me	Ph	Pr	0.44
Me	Ph	Bu	0.98
Me	Ph		0.36

[0019]

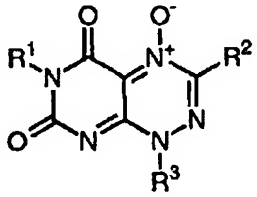
[Table 2]

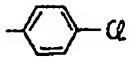
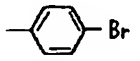
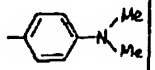
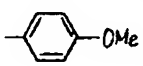


R¹	R²	R³	IC₅₀値(μg/ml)
Me		Me	0.29
Me		Me	0.28
Me		Me	0.50
Me		Me	0.44

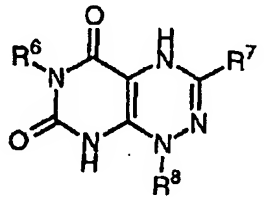
[0020]

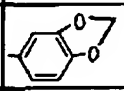
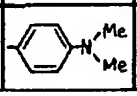
[Table 3]



R¹	R²	R³	IC₅₀値(μg/ml)
Ph	Ph	Me	0.91
Ph		Me	1.28
Ph		Me	2.01
Me		Me	0.28
Me	Ph	Me	0.63
Me		Me	0.77
Me		Me	0.55

[0021]
[Table 4]



R^6	R^7	R^8	IC_{50}値(μg/ml)	m. p. (℃)
Me	Ph	Me	1. 20	>219(dec.)
Me	Me	Me	0. 44	>175(dec.)
Me		Me	0. 65	>275(dec.)
Me		Me	0. 52	>250(dec.)

[Translation done.]